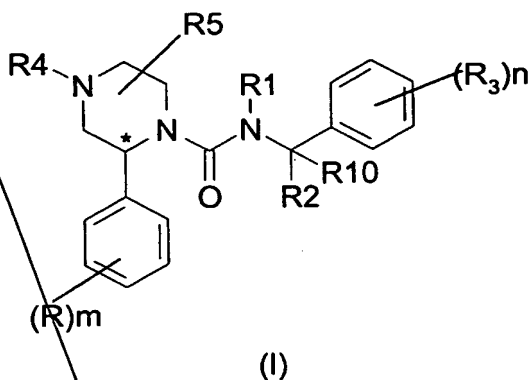


Claims

1. A compound of formula (I)



wherein

R represents a halogen atom or a C₁₋₄ alkyl group;

R₁ represents hydrogen or a C₁₋₄ alkyl group;

R₂ represents hydrogen, a C₁₋₄ alkyl, C₂₋₆ alkenyl or a C₃₋₇ cycloalkyl group; or R₁ and R₂ together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group;

R₃ represents a trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, a trifluoromethoxy or a halogen group;

R₄ represents hydrogen, a (CH₂)_qR₇ or a (CH₂)_rCO(CH₂)_pR₇ group;

R₅ represents hydrogen, a C₁₋₄ alkyl or a COR₆ group;

R₆ represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R₇ represents hydrogen, hydroxy or NR₈R₉ wherein R₈ and R₉ represent independently hydrogen or C₁₋₄ alkyl optionally substituted by hydroxy, or by amino;

R₁₀ represents hydrogen, a C₁₋₄ alkyl group or

R₁₀ together with R₂ represents a C₃₋₇ cycloalkyl group;

m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that, when R₁ and R₂ together with nitrogen and

carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine, and pharmaceutically acceptable salts. and solvates thereof.

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2. A compound as claimed in claim 1 wherein n is 2 and R₃ is trifluoromethyl both at the 3 and 5 position .

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3. A compound as claimed in claim 1 or claim 2 wherein R is selected independently from halogen or a C1-4 alkyl group and m is 1 or 2.

4. A compound as claimed in any of claims 1 to 3 wherein m is 2, R is selected independently from halogen or methyl group at 2 or 4 position.

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5. A compound as claimed in any of claims 1 to 4 wherein R₅ is hydrogen or a methyl group.

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6. A compound as claimed in any of claims 1 to 5 wherein R₁ is hydrogen or a methyl group.

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7. A compound as claimed in any of claims 1 to 6 wherein R₄ is hydrogen, a (CH₂)_rCO(CH₂)_pR₇ or CH₂)_qR₇ group, wherein R₇ represents an amine, both p and r are independently zero or 1; q is 1 or 2.

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8. A compound of formula (I) as claimed in any of claims 1 to 7, wherein R is selected independently from halogen or methyl, R₃ is trifluoromethyl both at the 3 and 5 position, R₁ is hydrogen or methyl, R₂ is hydrogen, methyl, 2-propenyl or a cyclopropyl group or together with R₁ is a 3,6-dihydro-2H-pyridin-1-yl, a piperidin-1-yl or a pyrrolidin 1-yl group, R₁₀ represents hydrogen, a methyl or R₁₀ together with R₂ is a cyclopropyl group, R₄ is hydrogen, an aminoacetyl or amino ethyl group and R₅ is hydrogen or a methyl group.

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9. A compound of formula (I) as claimed in any of claims 1 to 8, wherein R is selected independently from halogen or methyl and m is 2, R₃ is trifluoromethyl both at the 3 and 5 position, R₁ and R₂ are independently hydrogen or methyl, R₄ is hydrogen and R₅ is hydrogen.
- 5 10. A compound selected from:
- 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 10 2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 15 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;
- 2-(4-Fluoro-phenyl)-piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide;
- 2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide;
- 20 2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;
- 2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;
- 25 2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
- 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;
- 30 4-(2-Amino-acetyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide ;
- 2-(S)-(4-Fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

- 4-(2-Amino-ethyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(1-3,5-bis-trifluoromethyl-phenyl)-cyclopropyl]-methyl-amide;
 5 [2-(3,5-Bis-trifluoromethyl-phenyl)-pyrrolidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
 [2-(3,5-Bis-trifluoromethyl-phenyl)-3,6-dihydro-2*H*-pyridyn-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
 2-(3,5-Bis-trifluoromethyl-phenyl)-piperidin-1-yl]-[2-(S)-(4-fluoro-2-methyl-phenyl)-piperazin-1-yl]-methanone;
 10 2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-but-3-enyl]-methyl-amide;
 2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propyl]-methyl-amide;
 15 2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [(3,5-bis-trifluoromethyl-phenyl)-cyclopropyl-methyl]-methyl-amide;
 and enantiomers, pharmaceutically acceptable salts (e.g hydrochloride, methansulphonate, acetate) and solvates thereof.
- 20 11. 2-(S)-(4-Fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride.
12. 4-(2-Amino-acetyl)-2-(S)-(4-fluoro-2-methyl-phenyl)-piperazine-1-
 25 carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride.
13. 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide ethansulphonate.
- 30 14. 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide acetate.

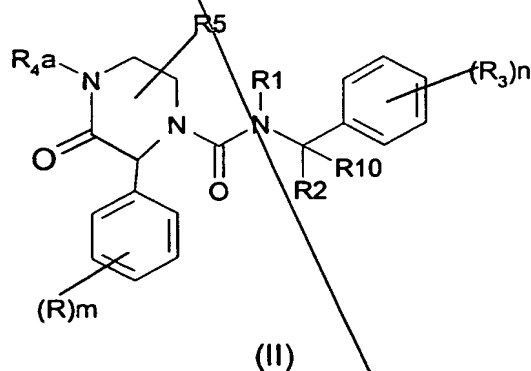
15. A compound as claimed in any of claims 1 to 14 for use in therapy.

16. The use of a compound as claimed in any of claims 1 to 14 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

17. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 14 in admixture with one or more physiologically acceptable carriers or excipients.

18. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound claimed in any of claims 1 to 14.

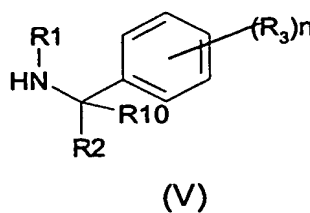
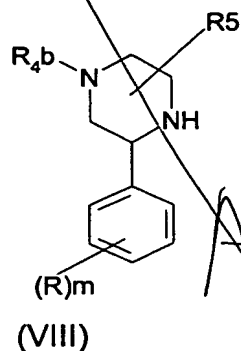
19. A process (A) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)_qR_7$ group, provided that when R_5 is a C_{1-4} alkyl or a COR_6 group, R_5 is not in the 3 position of the piperazine ring, which comprises reduction of a compound of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a $(CH_2)_qR_7$ group or protecting derivatives thereof; or



a process (B) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)_rCO(CH_2)_pR_7$ group which

comprises the reaction of a compound of formula (VIII), wherein R_{4b} represents a nitrogen protecting group or R_{4b} is $(CH_2)_r CO(CH_2)_p R_7$ or a protecting group thereof with triphosgene and an organic base followed by addition of the amine (V)

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followed where necessary or desired by one or more of the following step:

(i) removal of any protecting group;

(ii) isolation of the compound as salt thereof;

(iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

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Add
A²
Add
B¹²